PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-276WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB 03/03269	International filing date *(day/month/year)* 12.08.2003	Priority date *(day/month/year)* 14.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/20		
Applicant RANBAXY LABORATORIES LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.03.2004	29.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Luangkhot, N Telephone No. +49 89 2399-7857

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/03269

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-13 as originally filed

Claims, Numbers

1-43 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 37-42 with respect of industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 37-42 with respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-10,35,40,43
	No:	Claims	1-7,11-34,36-39,41-42
Inventive step (IS)	Yes:	Claims	8-10,35,40,43
	No:	Claims	1-7,11-34,36-39,41-42
Industrial applicability (IA)	Yes:	Claims	1-36,43
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the opinion

The formulation in claims 26,36 and 43 "wherein between 80% and 100% of the one or more active pharmaceutical ingredients in the extended release tablet is released over approx. 8 hours in both acidic ... and near neutral environment" does not delimit the scope of the protection to be sought and is rather to be construed as an attempt to define the invention by a **result to be achieved**. Therefore this effect would not be taken into account for the assessment of novelty (not inventive step).

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 37-42 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D4; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

2) Novelty according and inventive step to Art. 33(2) and 33(3) PCT

2a) The subject-matter of claims 1-7,11-34,36-39 and 41-42 is not novel and not inventive because D2 (see in particular Example 2, figure 1, claims 1,3,5-7) describes a sustained release tablet, which demonstrates uniformity of release rate over an acidic to nearly neutral pH range, containing:
a/ a drug
b/ a water swellable cellulose derivative such as hydroxyethylcellulose, or HPMC

(see claim 6)
c/ alginic acid derivative (see claim 7)
d/ a cationic polymer such as an acrylic polymer derivative such as Eudragit RS ou RL (see p.3 L.18-20)
Example 2 shows a composition wherein there is 11.1% of b/, 11.1% of c/ and 8.3% of d/. This disclosure anticipates the present claimed range of claims 12-14.

2b) The subject-matter of claims 8-10,35, 40 and 43 is novel because none of the cited prior art (e.g. D2) describes a tablet containing a/, b/, c/ and d/ as described above, characterized in that d/ is a cationic polymer comprising a methyl acid derivative with **a dimethylaminoethyl ammonium group**.

2c) The subject-matter of claims 8-10,35, 40 and 43 involves an inventive step for the following reasons:

- D1, which can be cited as the closest prior art, is directed to a sustained release tablet containing :
a/ a drug
b/ 10-40% of a water swellable hydrophilic polymer which can be a cellulose derivative or alginate (see claim 4 and col.11 L.24-25),
d/ cationic polymer comprising a methyl acid derivative with a dimethylaminoethyl ammonium group which is acid soluble and water swellable at higher pH.
The water swellable polymer of D1 which is exemplified is HPMC. Alginate, disclosed in a list, was not exemplified.
The difference consists in that present application uses combination of a cellulose derivative **and** an alginic acid derivative, whereas D1 employs preferably a cellulose derivative and can employ alginate.
The function attributed to the cellulose derivative and alginic acid derivative consists in that they are water swellable.

The effect obtained by the tablet of D1 and present application is a controlled release profile which presents uniformity of release rate over an acidic to nearly neutral pH range.

The problem to solved can be seen as providing an alternative tablet which shows

release rate which is independent on the pH and time.

D2 (see p.2 L.21-p.3 L.11) teaches that at low pH, HPMC swells, whereby controls the release rate of the drug while the formed gel layer erodes, whereas alginate is insoluble and thus blocks the release of the drug. At higher pH environment, the gel layer of HPMC is eroded, alginate swells and takes the role of HPMC which consists in controlling the release rate of the drug. Put in another words, D2 shows that alginate and HPMC behave differently in an acidic and in a neutral environment.

Therefore in view of the teaching of D2 the skilled man, willing to find an alternative, will not replace a cellulose derivative by alginate, nor will he use a combination thereof. The subject-matter of claims 8-10,35, 40 and 43 thus involves an inventive step over D1. Moreover the applicant shows with support of dissolution test that the release rate of present tablet is pH independent (see p.13 §1, fig.1 and 2).

- D3 (or D2), other document which can be taken as the closest prior art, describes a sustained release tablet, which demonstrates uniformity of release rate over an acidic to nearly neutral pH range, containing:
  a/ a drug
  b/ a water swellable cellulose derivative such as hydroxyethylcellulose, or HPMC (see claim 3)
  c/ alginic acid derivative (see claim 1)
  d/ an **enteric acrylic polymer** derivative such as Eudragit L/S (see claim 4, example on page 6) which is **soluble at high pH**.

The difference consists in d/: the acrylic polymer used.

The effect obtained by the tablet of D3 (or D2) and present application is a controlled release profile which presents uniformity of release rate over an acidic to nearly neutral pH range.

The problem to be solved can be seen as providing an alternative tablet which shows release rate which is independent on the pH and time.

The solution provided by the applicant is the use of an acrylic polymer as described in claims 8-10,35,40 and 43, which **is soluble at low pH** and swellable at higher pH. The said polymer has solubility property which is opposite to the polymer of D3 (or D2).

None of the cited prior art will impel the skilled man in the art to substitute the enteric polymer of D3 (or D2) with the polymer of claims 8-10,35,40 and 43 which has opposite solubility property. Thefore the subject-matter of claims 8-10,35, 40 and 43 thus involves an inventive step over D3 and D2. Moreover the applicant shows with support of dissolution test that the release rate of present tablet is pH independent (see p.13 §1, fig.1 and 2).

For the regional phase:

3) Clarity (Art. 6 PCT)

3a) The use of approximate terms such as "about" in claims 8-10,35,40 and 43 should be deleted because such terms introduce inexactness into quantities or expressions and so leave the reader in doubt as to the exact meaning of features qualified by such terms (see also Guidelines C-III 4.5a).

3b) **Claims 9-10 specify trade marks for which it may not be guaranteed that the composition of the product referred to is not modified while maintaining its name during the term of the patent.**
As they are not generally recognised as having a precise meaning and their use seems to be avoidable by including the composition thereof (see Guidelines CIII 4.5b and CII 4.16 and 4.17), they are not allowable according to Art. 6 PCT.

4) For the assessment of the present claims 37-42 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5) The attention of the applicant is drawn to the fact that the application may not be

amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 34(2)(b) PCT).

When filing amended claims the applicant should at the same time **bring the description into conformity with the amended claims**. Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 34(2)(b) PCT).

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.